

PRINCIPLES OF DIAGNOSTIC AND TREATMENT IN CERVICAL NEOPLASIA

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Abstract. According to the World Health Organization, cervical cancer ranks second in cancer in women, after breast cancer, as it represents 44% of the total feminine genital cancers. Every year 460,000 women all over the world are diagnosed with invasive cervical cancers and 200,000 women die by this illness. According to the data supplied by the Center for Health Statistics in Romania, over 66% of the new cases of cancer detected are between 35 and 55 years old, and about 70% of the deaths caused by cervical cancer is recorded for the women between 45 and 70 years old. The study was performed on a number of 1885 women aged between 20 and 85 years old, detected with cervical neoplasia in different stages in the County Hospital Galați. The cases studied showed a prevalence of cervical cancer of 37.3%. The profile of the patient showed that they come mainly from the urban area (77.3%), that about 80% of these women have a reduced educational level, and 23,6% are unemployed. The detected risk factors are: age, marital status, smoking, coffee consumption, alcohol, sex life debut, associated chronic diseases (high blood pressure, obesity), and contraceptives. In order to establish the diagnostic of cervical neoplasia the following examinations were performed: cytological smear, colposcopic examination, biopsy, histopathologic and complementary examinations. The comparison of the diagnostic methods allowed the doctors to establish how effective each of the conduct options is in the early detection of the serious changes, as these changes can progress towards cancer. They also wanted to see how acceptable every conduct option for the patients is; what is the cost/efficiency ratio for each option. The diagnostic certainty was accomplished through a histo-pathological examination of the material obtained by biopsy in comparison with colposcopy, with an accuracy of the method of 50.1%. We consider that patients with cervical cancer must not be abandoned, regardless of the stage of the cancer when they come to see the doctor, because sometimes, after a well-conducted complex treatment, the cases had a satisfactory evolution.

INTRODUCTION

Pathological manifestations appeared, of course, long before the humans did, in fact at the same time with the appearance of the living substance. The level of medical practice and knowledge has always been determined by the social conditions of that particular age, strongly correlated with the development of the whole society (Iancu 2009, SOGR 2010).

The research with a clinical, statistical, cytological, histological, histoenzymological and cytogenetic profile, and also the experimental studies made in the last 35 years have clearly proved the biologic and histogenetic potential of dysplasias, and also their value as cervical cancer precursors (ACOG 2010, Iancu et al 2010, IARC 2005, Mitchel 2006, Moss et al 2006, Sunnybrook Health Science Centre 2005, Wang et al 2009).

Neoplasia is one of the most complex and difficult problems of human pathology (ACOG 2004, ACOG 2009, ACOG 2010, Iancu 2009, SOGR 2010).

Cervical neoplasia is one of the main causes of death for the feminine population. It ranks second as frequency when it comes to feminine cancers (after breast neoplasia), so cervical cancer is appears worldwide in about 500,000 new cases and 200,000 new deaths every year (ACOG 2004, ACOG 2009, Acog 2010).

The incidence of cervical cancer in Romania in the last years places Romania on the second place in Europe. At the same time, Romania ranks first in Europe when it comes to cervical cancer mortality, 1500-1600 deaths every year (Iancu 2009).

Objective. The study seeks a better understanding of the natural history of cancer, intends to establish a more rigorous methodology for the screening programmes and also an objective appreciation of the effectiveness.

MATERIAL AND METHODS

The study lot consisted of a representative group, with a sample error of $\pm 2.25\%$ unlike $IC_{95\%}$, made of 1885 patients who were hospitalized in the period of time between 2007 and 2013 in The County Hospital Galați, having an average age of about 45 years old, 77.3% of which come from the urban area, with a reduced educational level. About 68% of the patients started their sexual life when they were younger than 19 years old, with an average number of pregnancies of about 3 pregnancies per patient, 61.8% of them being finalized by births. Their exposure to multiple partners when very young and “sexual pollution” increase the risk of getting viral infections of epithelia sensitive to carcinogens (basal,

cylindrical and reserve cells), which are not morphologically and functionally matured, and this aspect was highlighted in only 10% of the patients in the present study lot.

The specialty studies have not reached a unitary conclusion yet, as they could not certainly assess the degree of risk of oral contraceptives, because the duration of action either as an enhancer agent or as carcinogens is quite long. For this study lot 26.5% of the patients used oral contraceptives, generally the patients under 45 years old and/or the married women.

The theory that indicates tobacco consumption as an etiologic factor in the development of cervical dysplasias of high degree proves right. It has a relative risk that is over 2 times higher in older women and about 6 times higher for women coming from the urban area.

Coffee consumption (22.9%) showed a relative risk of cervical neoplasia 2.80 times higher for the patients under 45 years old, 1.57 times higher for unmarried patients and 4.78 times higher for the patients coming from the urban area.

Alcohol consumption was declared by 2.4% of the patients, being more frequent for the patients over 45 years old, unmarried and coming from the urban area. 80% of the women who consume alcohol are also smokers.

The screening methods were clinical examination and examination colpo-cervical-smear – they are based on the morphological study of the surface epithelium of the cervix, physiologically exfoliated and accumulated in the vaginal secretion from the posterior fornix. Detection must be understood in light of the time evolution of the tumor: process highlighting preclinical and clinical lesions. These aspects are also sustained by TNM classification, where the Tis N0M0 stage was introduced, curable in 100% of cases.

The early detection of cervical lesions requires a persistent concern of doctors and a certain educational level of women. If the detection is made in a moment in the pre-clinical evolution (incipient stage, stage 0), the mortality rate decreases and the invasive transformation of a lesion is avoided.

The detection of cervical lesions in an early stage of the carcinogenesis and an integrated approach of the clinical and cytological information, together with the adjustment of the diagnostic and therapeutic conduct, according to some largely accepted protocols, is the key for a decrease in the incidence of high degree lesions and invasive cancer. In countries where screening programs are conducted, they have proven effective, decreasing the incidence of cervical cancer a lot.

The most effective and widely used method, which is used in many countries in screening programs for cervical cancer, which can be carried out relatively easily on a large population, is the cervico-vaginal cytology. Generally, the Pap test is recommended to be performed regularly every three years between 21 and 65 age old or every three years at the debut of the sexual life, because most HPV infections are considered to be contacted in the first years of sexual life (18-25 years old). Liquid based cytology (LBC) helps to decrease the unsatisfactory cases significantly when compared to the conventional tests, thus reducing the need to repeat the sampling unnecessarily.

The conservative conduct recommends that cytology should be performed again. If the tests showed the presence of a lesion, it is recommended, if possible, to revise all the cytologic, colposcopic and eventually histo-pathologic evaluations made before. The patients will benefit from colposcopy and biopsy only if the repeated cytology suggested more severe changes.

If, during one of the examinations, the doctor finds the presence of a lesion that progresses colposcopically towards an aspect that suggests a high degree lesion or if the cytology is still H-SIL, it is recommended to use an excisional diagnostic method.

Surgical treatment (total extensive hysterectomy) is required after a thorough analysis of the case. Several factors need to be considered in this case: age, parity, desire to have children, desire to be sterilized, other medical problems, other gynecological problems associated, socio-economical factors. Yet, these factors need to be subordinated to the topographic and histopathologic aspects of the lesions and not to statistical data.

When the histopathologic examination of the resected sample confirms a high degree lesion or if conventional treatment was not successful, the patients have to be directed to oncology clinics, for a proper **radio and/or chemotherapeutic treatment**.

Strategies for combining chemotherapy with local treatment in cervical cancer:

- neo-adjuvant initial chemotherapy: indication – high failure rate because of the local treatment; motivation for association – the response of the tumour and/or an improvement of the local control by a subsequent local treatment;
- postoperative adjuvant chemotherapy: indication – remote microscopic metastases, common cause of failure after local treatment; motivation for association – micrometastases appear to be more sensitive to chemotherapy and can heal;
- radiosensitising chemotherapy: indication – radiotherapy alone can not provide local control; motivation for association – radiosensitivity growth, DNA repair, cell cycle modulating effect on free radicals.

Biopsy is the most important diagnostic method of the pre-neoplastic lesions, cervical intraepithelial neoplasia (CIN) and cervical carcinoma, no therapeutic plan being made without a biopsy examination.

Table I. the efficiency of biopsy

CYTOLOGIC RESULT *	NUMBER OF CYTOLOGIES	NUMBER OF BIOPSIES	% OF THE CYTO-DIAGNOSTIC
ASCUS	73	14	19.2
AGC	16	7	43.8
AGCNOS	199	121	60.8
ASCH	64	40	62.5
L-SIL	199	14	7.0
H-SIL	337	119	35.3
PAP III	109	29	26.6
PAP IV	314	254	80.9
PAP V	436	251	57.6

*Bethesda classification

The histo-pathological examination showed, for the 557 carcinomas:

- 291 patients with epidermoid carcinoma (52.2%)
- 16 patients with endometrial carcinoma (2.9%)
- 139 patients with pavementous carcinoma (25.0%)
- 87 patients with squamous carcinoma (15.6%)
- 22 patients with spino-cellular carcinoma (3.9%)
- 2 cases of papillary carcinoma (0.4%).

METHODS OF TREATMENT

The conservative conduct (prophylactic) consists of the treatment of chronic cervicitis, dysplasia, traumatic lesions, periodic checks, cytology, colposcopy, local and sexual hygiene (conization should be reduced to zero).

The share of the patients treated in a conservative way highlights the following aspects:

- 54.5% of the patients are over 45 years old;
- 73.7% of the patients come from the urban area;
- 68.6% of the patients are married;
- for 67.9% of the patients treated in a conservative way, the cyto-diagnostic showed a high degree;
- for 21.8% of the patients treated in a conservative way they performed colposcopy;
- biopsy was performed for 56.4% of the patients treated in a conservative way;
- to confirm the diagnosis, we checked the anatomo-pathologic samples harvested from 56.6% of the patients treated in a conservative manner.

Surgical treatment is required after a rigorous analysis of the case. Many factors will be taken into consideration, like age, parity, desire to have children, desire not to have children, other medical and gynecological problems associated, socio-economical factors. Still, these factors must be subordinated to the topographical and histo-pathological aspects of the lesions, and not to statistical data.

Classical surgical treatment consists of Wertheim-Meigs total enlarged (extensive) hysterectomy. The share of the patients treated surgically shows the following aspects:

- 66% of the patients are under 45 years old;
- 72.8% of the patients come from the urban area;
- 80% of the patients are married;
- for 66.7% of the patients treated surgically the cytodiagnosis was of high degree;
- for 34% of the patients treated surgically, initially the diagnosis was established by colposcopy;
- with a positive predictive value of 83,3%, biopsy preceded surgical treatment;
- for 82% of the patients the diagnosis of certainty was established by histopathology.

The oncologic treatment consists of radiotherapy (external and/or internal, pre and/or post operatory), chemotherapy, immunotherapy and hormone therapy.

The share of the patients sent for treatment in specialty oncologic services shows:

- 51.5% of the patients are under 45 years old;
- 84.6% of the patients come from the urban area;
- 81.4% of the patients are married;
- for 64,4% of the patients treated oncologically the cytodiagnosis was of high degree;
- after the histopathologic diagnosis was established 20.7% of the patients were sent to oncology clinics for specialty treatment.

DISCUSSION

Many studies and data in literature underline once again the remarkable importance of the cytological examination, which contributed to a larger number of cases being detected and diagnosed in the early pre-invasive stage than the number of cases that are detected in the invasive stage (ACOG 2009, Iancu et al 2010, Mitchell 2006, Moss et al 2006, Wang et al 2009). Women who have never had a Pap test (cytologic examination), or who had one many years ago, have a higher risk than the average of developing cervical cancer (Bayo et al 2002).

Based on the cases studied by conventional cytology (Papanicolau classification), the cytology was very suggestive for malignancy for 31.7% of the patients and for 44.2% of them it showed a conclusive cytology for malignancy.

The colposcopic examination was performed for 359 patients (19%) and the results were certain for 97.5% samples examined.

For 32% of the patients with L-SIL the colposcopic evaluation confirmed minor changes; 11.1% of the patients with H-SIL had minor changes detected by colposcopic exam and 15.6% had major changes.

When the modern means of investigation - colposcopy, cytologic examination – were introduced, that allowed the diagnosis to be established in earlier and earlier stages of the disease, the infraclinical or paraclinical stages, such as intraepithelial cancer, micro-invasive cancer and microcancer (Chan et al 2009).

The diagnostic certainty was accomplished by histopathologic examination of the sample obtained in biopsy, with an accuracy of the method of 50.1%.

The conservative conduct is represented by the repeated cytology when the patients are admitted in the lot (the initial cytology had been performed before this moment). The patients were performed colposcopy and biopsy only if the repeated cytology suggested more severe changes.

The immediate colposcopy, followed by biopsy if needed, represents an aggressive manner of treatment (IARC 2005, Sunnybrook Health Science Centre 2005).

CONCLUSIONS

Where the conservative conduct was applied, the patients were performed colposcopy and biopsy only if the repeated cytology suggested more severe changes.

The introducing of the modern means of investigation - colposcopy, cytological examination, biopsy – allowed and earlier and earlier diagnostic in the incipient stages of the disease, infraclinical or subclinical, like intraepithelial cancer, micro-invasive cancer and microcancer.

The diagnostic certainty was accomplished through the histo-pathological examination of the material obtained by biopsy in comparison with colposcopy, with an accuracy of the method of 50.1%.

REFERENCES

- ACOG Committee Opinion #300** (2004). *Cervical cancer screening in adolescents*. *Obstet Gynecol*, 104: 885.
- ACOG Practice Bulletin No. 109** (2009). *Cervical cytology screening*. *Obstet & Gynec*; 114(6): 1409-1420.
- ACOG Committee Opinion No. 463** (2010). *Cervical cancer in adolescents: screening, evaluation, and management*. *Obstet Gynecol*; 116:4 69–72.
- Bayo S, Bosch FX, De Sanjose S et al** (2002). *Risk factors of invasive cervical cancer in Mali*. *Int. J. Epidemiol*, February 1; 31(1): 202 - 209.
- Chan BKS, Melnikow J, Slee CA, Arellanes R, Sawaya GF** (2009). *Posttreatment human papillomavirus testing for recurrent cervical intraepithelial neoplasia: a systematic review*. *Am J Obstet Gynecol*; 200: 422.e1-422.e9.
- Iancu Doina, Crauciuc E, Pricop Florentina** (2001). *Cervical neoplasia and the early debut of the sexual life*. *Bul Perinatol, Chişinău*, 4: 17-20.
- Iancu Doina, Eduard Crauciuc, Ovidiu Toma, Dragos Crauciuc** (2010). *Histopathologic diagnostic of the cervix neoplasm*. *Scientific Annals of Alexandru Ioan Cuza University, Department of Genetics and Molecular Biology*; XI(1): 55-61.
- Iancu Doina, Eduard Crauciuc, Ovidiu Toma, Dragos Crauciuc** (2010). *The cytological diagnostic of cervical cancer*. *Scientific Annals of Alexandru Ioan Cuza University, Department of Genetics and Molecular Biology*; XI(1): 49-55.
- Iancu Doina** (2009). *General aspects of cervical cancer*. Junimea Publishing House Iaşi; ISBN 978-973-37-1374-6.
- International Agency for Research on Cancer (IARC)** (2005). *Colposcopy and treatment of cervical intraepithelial neoplasia: a beginner's manual*. <http://screening.iarc.fr/colpochap.php?lang=1&chap=1>.
- Mitchell HS** (2006). *Laboratory performance measures: evidence against low-risk women explaining low detection rates of high-grade abnormalities*. *Updated cancer information, Cytopathology*; 17:4 210.
- Moss Sue, Alastair Gray, Rosa Legood et al** (2006). *Liquid Based Cytology/Human Papillomavirus Cervical Pilot Studies Group - Effect of testing for human papillomavirus as a triage during screening for cervical cancer: observational before and after study*, *BMJ*, Jan 2006.
- SOGR, Colegiul Medicilor din România** (2010). *Cancerul de col uterin*. Ghidul 32/Revizia O, 02.12.2007. Buzău, Alpha MDN.
- Sunnybrook Health Science Centre** (2005). *Colposcopy: abnormal results*. <http://www.colposcopy.com/ab-res.html>.
- Wang S, Lang JH, Cheng XM** (2009). *Cytologic regression in women with atypical squamous cells of unknown significance and negative human papillomavirus test*. *Am J Obstet Gynecol*; 201: 569.e1-6.

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